Outcome of lung transplantation for patients requiring concomitant cardiac surgery

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Background: The clinical results of lung transplantation and concomitant cardiac surgery are unclear. The effect of cardiopulmonary bypass on the pulmonary allograft is controversial, and the effect of cardiac arrest and cardiac surgery in this setting is unknown. Our aim was to review the operative results and long-term survival in this group of patients.

Methods: A retrospective review of all lung transplantations between 1988 and 2003 was performed. Patients who had concomitant cardiac surgery during lung transplantation were compared with those who underwent lung transplantation alone. The variables analyzed included allograft ischemic times, use of cardiopulmonary bypass, early graft dysfunction, postoperative morbidity, survival, length of mechanical ventilation, length of stay in the intensive care unit, and overall hospital stay.

Results: During this period, 35 of 700 lung transplant recipients (15 single and 20 bilateral transplantations) underwent concomitant cardiac surgery. The cardiac procedures were for patent foramen ovale (n = 18), atrial septal defect (n = 9), ventricular septal defect (n = 2), coronary bypass (n = 4), and "other" (n = 2). Allograft ischemic time, use of extracorporeal membrane oxygenation, length of hospital stay, operative mortality, and survival were not significantly different between the 2 groups. Ventilator time and intensive care unit stay were longer in the cardiac surgery group.

Conclusions: Cardiac surgery at the time of lung transplantation can be performed with acceptable morbidity and mortality. The immediate and long-term survival in these patients is similar to that of other lung transplant recipients. Lung transplantation should continue to be offered to patients with normal ventricular function who require concomitant limited cardiac surgery.

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Over the past two decades, lung transplantation has become an effective treatment for a variety of end-stage lung diseases. Advances in surgical techniques, preservation of ischemic allografts, immunosuppression, and management of infectious complications have steadily improved the results of lung transplantation. Nonetheless, organ donor shortage and long waiting lists have precluded patients with other serious comorbidities to be considered for lung transplantation. These patients traditionally have been denied lung transplantation to maximize favorable patient outcomes.

Comorbidity from underlying cardiac disease is one such factor that has potentially prohibitive surgical risks and poses a difficult clinical challenge. Although use of cardiopulmonary bypass (CPB) during lung transplantation might allow for controlled reperfusion of the lung, it also can have several potential adverse sequelae, including increased bleeding, increased cytokine expression and activation of the complement system, and endothelial damage. Addition of cardiac arrest, with

TABLE 1. Univariate analysis of preoperative characteristics between groups

	Lung transplantation only (n = 665)	Concomitant cardiac surgery (n = 35)	*P* value
Age (y)	48 ± 12	40 ± 12	<.001
Sex (female)	335 (50.3%)	19 (54.3%)	.730
Diagnosis			<.001
COPD	385 (57.9%)	4 (11.4%)	
Cystic fibrosis	113 (17.0%)	2 (5.7%)	
Pulmonary hypertension	37 (5.6%)	26 (74.3%)	
IPF	76 (11.4%)	3 (8.6%)	
Other	54 (8.1%)	0	
Waiting time (d)	551 ± 372	536 ± 337	.816

COPD, Chronic obstructive pulmonary disease; *IPF,* idiopathic pulmonary fibrosis.

its known increase in the inflammatory response, can further increase morbidity and mortality after lung transplantation.[1,2] We reviewed our experience in patients who underwent a concomitant cardiac procedure during lung transplantation to determine the morbidity and early and late mortality associated with this approach.

Methods

Patients

A retrospective review of all lung transplantations at our institution between January 1988 and August 2003 was performed. Of the 700 patients who underwent lung transplantation, 35 (0.5%) were identified who underwent concomitant lung transplantation and cardiac surgery. Background characteristics of the patients who underwent concomitant procedures in comparison with the patients who underwent isolated lung transplantation are as shown in Table 1.

Operative Procedure

A total of 15 unilateral and 20 bilateral lung transplantations were performed in the patients who had a concomitant cardiovascular procedure. The majority of cardiac procedures were for repair of congenital intracardiac septal defects (Table 2). All the procedures were done with CPB, and the cardiac procedure was performed before the implantation of the lungs. CPB was continued during lung implantation. Need for extracorporeal membrane oxygenation (ECMO) was clinically determined intraoperatively if, after all standard maneuvers for alveolar recruitment, optimization of ventilation and administration of nitric oxide had failed and there was evidence of significant graft dysfunction manifested by persistently low Pao_2. Usually, there were several problems addressed by the use of ECMO: hypoxemia, hypercarbia, respiratory acidosis, and stiff lung mechanics with very high airway pressures. There were no standard criteria for use of ECMO on any one of these factors, but a clinical impression was made on the basis of all of them simultaneously.

TABLE 2. Description of the type of elective concomitant cardiac surgery performed

Type of cardiac surgery performed	N
Patent foramen ovale closure	18
Atrial septal defect repair	9
Ventricular septal defect repair	2
Coronary artery bypass (single vessel)	4
Pulmonary artery aneurysmectomy with reconstruction	1
Replacement of ascending aorta	1

Morbidity, Mortality, and Long-Term Survival

Morbidity data were collected from our lung transplantation database that documents all adverse outcomes on the basis of prospective data collection from the patient's clinical records. Early graft dysfunction was defined as a Pao_2/inspired fraction of oxygen of 150 or less on initial or 24-hour arterial blood gas measurement. Acute renal failure was defined as doubling of the serum creatinine concentration compared with baseline values without the need for renal replacement therapy. Coagulopathy was defined as persistent abnormalities in the partial prothrombin time or prothrombin time, a platelet count of less than 100,000/mm^3, or both, in the presence of active bleeding requiring transfusions. Sepsis was defined as a persistent increase in the white blood cell count and concomitant hypotension requiring treatment with vasopressors and antibiotics, with or without associated fever. Finally, myocardial infarction was based on enzymatic increases of creatine phosphokinase or troponin above normal values, with or without associated electrocardiographic changes.

The cohort that underwent the concomitant procedures was compared with the rest of the patients who had isolated lung transplantation. The variables analyzed included ischemic times, length of mechanical ventilation, length of stay in the intensive care unit (ICU), length of stay in the hospital, and overall hospital mortality. Long-term survival between the 2 groups was also analyzed.

This study was approved by the Institutional Review Board of Washington University School of Medicine.

Statistical Analysis

Descriptive statistics were expressed as means ± standard deviation unless otherwise specified. Categorical data were expressed as counts and proportions. Comparisons were done with unpaired, 2-tailed *t* tests for means of normally distributed continuous vari-

TABLE 3. Univariate analysis of postoperative outcomes between groups

	Lung transplantation only (n = 665)	Concomitant cardiac surgery (n = 35)	*P* value
Bilateral transplantation	504 (75.9%)	21 (57.1%)	.032
Ischemic time (min)	285.8 ± 66.5	296.8 ± 70.7	.342
Use of CPB	123 (18.4%)	35 (100.0%)	<.001
ECMO required	17 (2.6%)	3 (8.6%)	.073
Mortality	49 (7.4%)	4 (11.4%)	.328

CPB, Cardiopulmonary bypass; *ECMO,* extracorporeal membrane oxygenation.

ables and the Wilcoxon rank sum test for skewed data. Fisher exact or χ^2 tests were used to analyze differences among the categorical data. Kaplan-Meier estimates were used to depict survival. Cox multivariate proportional hazards regression was used to adjust for confounding variables that were found to be different between the groups in univariate testing to further examine survival after transplantation. All data analysis was performed with SPSS (SPSS 11.0 for Windows; SPSS Inc, Chicago, Ill).

Results

Univariate Analysis

The mean age of patients undergoing combined cardiac procedures and lung transplantation was lower than that of patients who underwent isolated lung transplantation (40 ± 12 vs 48 ± 12 years, $P < .001$). The most common indication for transplantation was chronic obstructive pulmonary disease in 57.9% of patients undergoing isolated lung transplantations, whereas 74.3% of the patients had pulmonary hypertension in the cohort who had the combined procedure ($P < .001$). In the pulmonary hypertension group, primary pulmonary hypertension was present in 14 of the 26 patients, all of whom had patent foramen ovale (PFO) repair during lung transplantation. In the remaining 12 patients, pulmonary hypertension was associated with a preexisting congenital cardiac anomaly. Other preoperative factors, such as sex and time spent on the waiting list, were not significantly different between the 2 groups (Table 1).

Of the patients who underwent combined procedures, 20 (57.1%) of 35 had bilateral lung transplantations in comparison with the other cohort in which the large majority of the patients underwent bilateral lung transplantations (505/665 [75.9%]). The mean allograft ischemic time for both groups of patients was not significantly different (285.8 ± 66.5 minutes for the isolated lung transplantation group vs 296.8 ± 70.7 minutes for the combined group, $P = .342$). Although CPB was used in all the patients undergoing concomitant cardiac procedures, only 20% of the cases of isolated lung transplantation required use of CPB. The use of ECMO and in-hospital mortality were higher in the patients with the combined procedures compared with those undergoing isolated lung transplantations (Table 3).

Morbidity and Mortality

There were 4 (11.4%) in-hospital deaths in the patients who underwent a combined procedure. Two died of primary graft failure, 1 died of a cerebrovascular accident, and 1 died of intraoperative hemorrhage. The patient who died of intraoperative hemorrhage had undergone a prior repair of an aortic coarctation with significant adhesions related to his previous operation. During dissection, an inadvertent tear in the ascending aorta necessitated urgent establishment of CPB for replacement of the ascending aorta.

The patients undergoing combined procedures had a significantly longer requirement for postoperative mechanical ventilation, with a median time of 5 days on the ventilator, compared with the patients undergoing isolated lung transplantations, who had a median time of 2 days ($P < .001$). Patients undergoing cardiac surgery also had a longer stay in the ICU compared with the other group, with a median stay in the ICU of 6 days compared with 3 days ($P < .001$). However, overall length of stay in the hospital was similar between the 2 cohorts ($P = .355$, Figure 1).

Table 4 lists postoperative complications in patients undergoing concomitant cardiac surgery. The most common complication was supraventricular arrhythmias (37.1%),

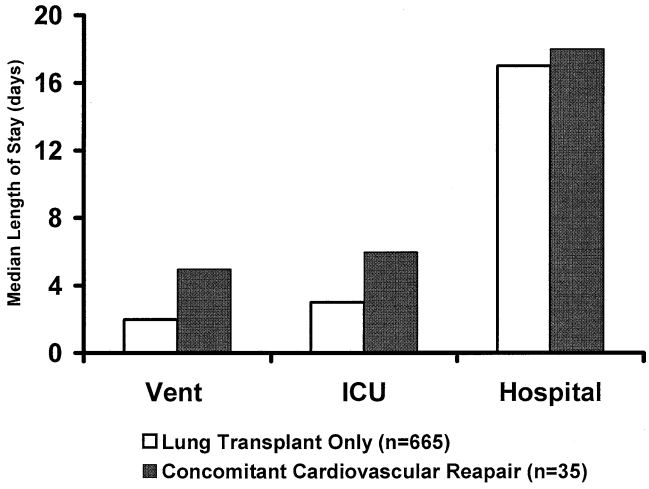

Figure 1. Posttransplantation hospitalization.

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TABLE 4. Description of the postoperative morbidity in the concomitant cardiac surgery group

Hospital morbidity	N (%)
Dysrhythmia	13 (37.1%)
Early graft dysfunction	10 (28.6%)
Acute renal failure	8 (22.9%)
Reexploration for bleeding	8 (22.9%)
Required reintubation	7 (20.0%)
Coagulopathy	5 (14.3%)
Sepsis	2 (5.7%)
Myocardial infarction	2 (5.7%)

followed by primary graft failure (28.6%). Reexploration for bleeding was required in 8 (22.9%) patients.

Long-Term Survival

The survival in the patients who underwent isolated lung transplantations was 84.9% at 1 year, 72.3% at 3 years, and 57.0% at 5 years. This was not significantly different from the survival in the cohort that had concomitant cardiac surgery and lung transplantation, which showed a survival of 77.1% at 1 year, 66.7% at 3 years, and 54.2% at 5 years (Figure 2). In a Cox multivariate analysis, adjusting for age and diagnosis, concomitant cardiac surgery was not found to be a predictor for decreased survival. To account for the large number of patients who had closure of a PFO as the primary cardiac operation, we repeated the survival analysis by dividing the concomitant cardiac surgery group into those who had closure of a PFO and those who had other operations. There were no differences in survival at 5 years among the various subgroups: 56.9%, 48.7%, and 62.5% for isolated lung transplantation, other concomitant cardiac surgery, and concomitant PFO closure, respectively (P = .330). Furthermore, analyzing the survival of patients with concomitant cardiac surgery and lung transplantations on the basis of 2 separate eras (before 1995 and after 1995) to account for the shift in our practice to perform double-lung transplantations failed to identify any survival difference between the 2 groups: 61.1% at 5 years for those undergoing transplantation before 1995 and 44.6% at 5 years for those undergoing transplantation from 1995 and beyond (P = .472).

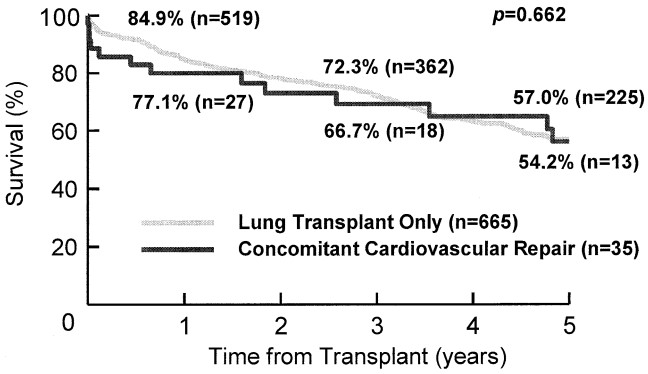

Figure 2. Kaplan-Meier survival after lung transplantation stratified by those who underwent lung transplantation only and those who underwent a concomitant cardiac surgical procedure with the lung transplantation.

Discussion

Lung transplantation has become an accepted treatment for end-stage lung disease over the past 2 decades. Concomitant cardiac surgery during lung transplantation might increase the perioperative morbidity associated with this procedure. Our data suggest that patients who require limited cardiac surgery at the time of lung transplantation have an acceptable morbidity and mortality, with early and long-term survival similar to that of patients undergoing isolated lung transplantation. Lung transplantation should continue to be offered to patients with normal ventricular function who require concomitant limited cardiac surgery.

Previous studies have reported mixed results with use of CPB during lung transplantation.[2-5] Indications for use of CPB generally depend on the presence of significant pulmonary hypertension, the ability to tolerate single-lung ventilation, and other intraoperative factors.[6] Concerns regarding the use of CPB include the need for heparinization and the increased risk of bleeding and transfusion requirements. In addition, other recognizable disadvantages include the upregulation of the inflammatory response and the possibility of increased permeability of the pulmonary capillary bed. Despite these limitations, several studies suggest that CPB might have immunomodulating effects and actually improves outcomes in HLA-mismatched patients.[4] The addition of a cardiac surgical procedure with use of CPB might further potentiate the inflammatory response.[7,8] Given these concerns, the purpose of this retrospective study was to determine whether addition of a cardiac surgical procedure to an already complex operation would increase the morbidity and mortality of lung transplantation. In this group we found a longer duration of ventilatory support and ICU stay, a 23% incidence of reexploration for bleeding, and a 29% incidence of early graft dysfunction. The overall incidence of primary graft dysfunction at our institution is 22%, and the incidence is highest in the patients who undergo transplantation for primary pulmonary hypertension.[9] In addition, longer duration of ventilatory support and ICU stay is more common in this subgroup.[9] Given that 74% of the patients who had cardiac surgery had underlying primary pulmonary hypertension as the reason for lung transplantation, our results are not surprising. However, previous reports on patients undergoing bilateral lung transplantation with CPB have shown an increased inci-

dence of early graft dysfunction.[3] In those patients, early and late mortality were not different, which is similar to our data. Similarly, Pigula and colleagues[10] reported their experience with 30 patients, of which 23 had a combined procedure and 7 had a history of cardiac procedures for repair of congenital anomalies. In their experience, mortality was 23% (7/30), and the long-term survival of the patients who survived was similar to that of the group that underwent heart-lung transplantation for congenital heart disease. The authors concluded that by doing the combined procedure of fixing the congenital heart disease and lung transplantation, they expanded the donor pool because otherwise these patients would require combined heart-lung transplantation. This approach has been adopted in the pediatric population; however, it has not been used in the adult patient with congenital heart disease.[11]

Coronary artery disease was previously considered an absolute contraindication for lung transplantation. The true incidence of coronary artery disease in the patients considered for lung transplantation is not known; however, risk factors such as smoking are common in patients with end-stage lung disease and can lead to a significant increase in the incidence of coronary artery disease in potential lung recipients. As a result, cardiac catheterization is routinely performed at our center as part of evaluation for consideration of lung transplantation.

Recently, we have performed transplantations in patients with normal ventricular function and limited coronary artery disease with good results and no complications related to the coronary artery disease.[12] Although all our patients underwent a single-vessel bypass, the group at Duke has reported good outcomes in patients who underwent 2- and 3-vessel bypass.[13]

The primary limitation of this study, as with most uncontrolled analyses, is the selection bias for patients who underwent cardiac surgery during lung transplantation. Clearly, data on patients who were refused because of more complex anatomy or other cardiac comorbidities were not available. Despite the small sample size, we conclude that for patients with adequate ventricular reserve, cardiac surgery can be performed during lung transplantation with acceptable morbidity and mortality and good long-term survival.

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